REMARKS

The specification is amended to update the status of the parent application.

In view of the examiner's remarks with respect to the election of species, and/or in view of preferences cited in the specification, the generic scope of compounds claimed for use in the method of the invention is amended. Because of the substantial amount of material to be deleted from the scope of the compounds as a result of the amendment, rather than amending claims 19 and 20 by extensive crossing-out, applicants have canceled claims 19 and 20 and have replaced them with new claims 21 and 22.

In claims 21 and 22, the definitions of Z^1 and Z^2 were amended to correspond to the preferences for compounds identified in the specification on page 7, lines 5-6, i.e., Z^1 and Z^2 are each R^7-aryl. This scope is similar to the elected species, but narrower than the expanded scope searched by the examiner.

The definitions of R^1 to R^4 were also amended to correspond to the preference identified in the application on page 5, lines 9-10; this preference corresponds to the elected species and the scope of the expanded search.

In view of the restriction requirement, applicants have amended the scope of the "X" groups to delete compounds wherein X^1 is a bicyclic group and X^2 is hydrogen, and compounds wherein X^1 and X^2 form a spiro group.

As a result of the amendments to the X and Z variables, the variables m, n, p, q, r, w, u, Q, R^{11}, R^{12}, R^{16}, R^{17}, R^{23}, R^{24} and R^{28} are no longer necessary and were deleted. The provisos at the end of the claim relating to the Z groups are also no longer necessary and were deleted.

In view of the amended scope of the generic formula in claims 21 and 22, claims 2, 5, 6 and 9-12 have been canceled.

Claim 3 is amended to correct its dependencies in view of the replacement of claim 19 with claim 21.

Claim 7 is amended to replace the term "-NC(O)R^{21}" with the term "-NHC(O)R^{21}" to account for the third valence on the nitrogen atom, to amend the dependency in view of the cancellation of claim 19, and to delete a duplicate "and".

No new matter has been introduced by the requested amendments, and no change in inventorship is required. Applicants reserve the right to file divisional or continuation applications to the non-elected subject matter.

Claim 7 was rejected under 35 U.S.C. 112, second paragraph, for indefiniteness in the use of the term "-NC(O)R^{21}" because only two attachments to the atom are shown. While applicants believe that one skilled in the art would realize that a hydrogen atom is understood, applicants have amended the term to read "-NHC(O)R^{21}". The rejection states that claim 19 does not have a group consistent with this term, but applicants point out that the definition of X^2 in claim 19 (replaced by claim 21) refers to the group $-(CH_2)_vNHC(O)R^{21}$, which corresponds to the amended group in claim 7 when v is 0.

Reconsideration and withdrawal of the rejection under 35 U.S.C. 112, second paragraph, are respectfully requested.

Claims 19, 20 (hereafter referred to as replacement claims 21 and 22), 2-4 and 6 were rejected under 35 U.S.C. 103 as being unpatentable over Casy et al in view of Chang et al in combination with Shum et al.

Applicants confirm that the subject matter of the claims was commonly owned at the time the inventions were made.

Casy et al disclose nociceptive *opioid* 8-azabicyclo[3.2.1]octanes; they do not disclose ORL-1 activity or the treatment of cough. The present application claims the previously unknown treatment of cough with combinations comprising an ORL-1 agonist; ORL-1 agonists, previously known for the treatment of pain (nociception) do not produce the undesirable side effects of traditional opioids (see the specification on page 2, second paragraph). Applicants note that the amended scope of compounds claimed for use in the method and combination of the present invention does not overlap with the scope of compounds disclosed by Casy et al, since the presently claimed "Z" groups must be di(R^7-phenyl)methyl, optionally substituted on the methyl portion with an alkyl group, while the Casy et al compounds have H, alkyl or ethylphenyl substitution at the corresponding position.

Casy et al alone does not teach or suggest the presently claimed method or combination for treating cough with a genus of ORL-1 agonist compounds and

another agent for treating cough, since it cannot be said to disclose the use of structurally different compounds for an undisclosed method of treatment.

Chang et al teaches opioid agonists and discloses their use in treating cough. However, the compounds claimed by Chang et al do not overlap in scope with the compounds included in applicants method or combination claims. The Chang et al compounds can have a diphenylmethyl substituent, but at the 4-position of the piperidinyl ring, not on the nitrogen, and applicants compounds do not comprise a sole diphenylmethyl substituent at the 4-position of the piperidinyl ring. The Chang et al compounds are disclosed to have delta and/or mu receptor activity; mu receptor activity is known to be associated with the treatment of cough (e.g., codeine is a mu-receptor) but it is also known to be associated with the undesirable side effects (e.g., tolerance, addiction) of opioid agonists; as indicated above, the ORL1-agonist activity of the compounds in the instant method claims does not result in those side effects. Applicants cannot locate any reference in Chang et al to combinations with other active ingredients

The rejection refers to Ito et al as the reference with which Chang et al is combined, rather than Casy et al. Ito et al is not one of the references cited against the present application under 35 U.S.C. 103(a) on page 4 of the rejection, and applicants presume that the rejection should have referred to Casy et al. If however, the rejection was referring to WO 99/36421 (Ito et al, cited in the IDS), applicants point out that as amended, the compounds included in the instant claims do not overlap with the compounds of Ito et al, which require the compounds to have a bicyclic group at the 4-position of the piperidinyl ring. While the Ito et al compounds are identified as ORL-1 agonists, cough is not an indication.

Shum et al, which claims a process for preparing guaifenesin, was cited as teaching the use of guaifenesin in the treatment of cough. Applicants do not dispute that guaifenesin is known to treat cough, especially since they list it as an example of an expectorant in the specification and elected it for the combination to be searched. However, Shum et al do not teach or suggest the combination of guiafenesin with an ORL-1 agonist to treat cough.

Chang et al and Shum et al cannot cure the deficiencies of Casy et al in rendering the present invention unpatentable. Casy et al disclose ORL-1 agonists, but not for treating cough, and not in combination with other agents for treating cough. Chang et al claim compounds that are opioid agonists, a pharmacological mechanism long known to treat cough, but do not mention ORL-1 agonist activity. Shum et al disclose a process for preparing guaifenesin, a compound known in the treatment of cough. At best, the combination of Chang et al and Shum et al might be said to suggest that opioid agonists can be used in combination with guaifenesin, although there is no real basis in the references for that conclusion, since neither reference discloses combinations. Assuming that the combination of Chang et al and Shum et al could be used to demonstrate that combination, the combination of references still should not be combined with Casy et al, since references teaching different compounds having a different use and not teaching combinations cannot be properly combined to render the instant combination claims unpatentable.

Applicants further point out that the compounds in the method and combination claims of the present application have been patented in the original priority application (US 6,262,066). Since the compounds are novel, it is respectfully urged that methods and combinations comprising those compounds are also novel. Since no one had identified the compounds in the present method and composition claims prior to applicants, combinations comprising those compounds could not have been contemplated .

Reconsideration and withdrawal of the rejection under 35 U.S.C. 103(a) are respectfully requested.

Respectfully submitted,

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Date

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